Universitätsspital Zürich
Klinik für Neurochirurgie
Direktor: Prof. Dr. med. Luca Regli

Betreuung der Masterarbeit: Dr. med. Giuseppe Esposito
Leitung der Masterarbeit: Prof. Dr. med. Luca Regli

Repeated neuroimaging after spontaneous, non-perimesencephalic subarachnoid hemorrhage with initially negative angiogram: what kind of neuroimaging is needed, and when?

MASTERARBEIT

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Jean-Philippe Dufour (13-937-289)

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1. SUMMARY

INTRODUCTION

In approximately 15% of patients with spontaneous subarachnoid hemorrhage (SAH) a bleeding source is not determined in the initial neurovascular imaging. These patients are commonly categorized based on CT blood distribution into a perimesencephalic group and a non-perimesencephalic group (NPM-SAH), which is the subject of this study. Follow-up imaging is routinely performed in patients with spontaneous, angiogram-negative NPM-SAH to rule out a treatable etiology. However, the optimal follow-up imaging protocol for these patients remains unclear. Here, we examine the time to re-imaging after bleeding and the value of magnetic resonance angiography (MRA) in this setting.

METHODS

In this single-center, retrospective study, the medical records of patients treated at the University hospital of Zurich from 2007 to 2016 with NPM-SAH were analyzed and demographical, clinical and radiological data was collected. The re-imaging data was grouped according to imaging modality and into three categories according to time since bleeding: short-term (0-2 weeks), medium-term (2-8 weeks) and long-term (after 8 weeks).

RESULTS

30 patients with spontaneous, angiogram-negative NPM-SAH who received re-imaging were included in this study. Re-imaging revealed three true aneurysms, resulting in a diagnostic yield of 10.0%. All three aneurysms were detected during the period of medium-term re-imaging, which was defined as 2-8 weeks after bleeding, and all three aneurysms were visible both on MRA and on digital subtraction angiography (DSA). The negative predictive value of DSA and MRA at day 14 post-bleeding was 85.7% and 91.3% respectively, and reached 100% for both imaging modalities at 8 weeks post-bleeding. Re-imaging led to two false-positive findings in which surgical exploration was negative, which resulted in a positive predictive value of 75% for MRA and 50% for CTA at 8 weeks.

CONCLUSIONS

We propose re-imaging for NPM-SAH patients during the periods of 10-14 days and 6-8 weeks after bleeding. We suggest high-quality 3 Tesla MRA as a possible non-invasive alternative to DSA for re-imaging after NPM-SAH. In re-imaging after NPM-SAH, suspect or unclear findings on CTA or MRA should be corroborated on a DSA examination before performing surgical exploration to avoid false-positive findings. Long-term radiological follow-up after 8 weeks post-bleeding is unlikely to be of diagnostic benefit.

2. LIST OF ABBREVIATIONS

ACA	Anterior Cerebral Artery
ACommA	Anterior Communicating Artery
CTA	Computer Tomography Angiography
DCI	Delayed Cerebral Ischemia
DSA	Digital Subtraction Angiography
EVD	Extraventricular Drain
GCS	Glasgow Coma Scale
GOS	Glasgow Outcome Scale
HCP	Hydrocephalus
IA	Intracranial Aneurysm
ICA	Internal Carotid Artery
ICU	Intensive Care Unit
LD	Lumbar Drainage
MCA	Medial Cerebral Artery
MRA	Magnetic Resonance Angiography
MRI	Magnetic Resonance Imaging
NPM-SAH	Non-perimesencephalic Subarachnoid Hemorrhage
NPV	Negative Predictive Value
PCA	Posterior Cerebral Artery
PCommA	Posterior Communicating Artery
PM-SAH	Perimesencephalic Subarachnoid Hemorrhage
PPV	Positive Predictive Value
SAH	Subarachnoid Hemorrhage
TOF-MRA	Time-of-Flight Magnetic Resonance Angiography
UIA	Unruptured Intracranial Aneurysm
USZ	University Hospital of Zurich
VBA	Vertebrobasilar Arteries
VP-Shunt	Ventriculoperitoneal Shunt
WFNS	World Federation of Neurosurgeons Scale

3. INTRODUCTION

3.1. Cerebral Aneurysms

Aneurysms are pathological, localized bulging areas of blood vessels. Intracranial aneurysms (IAs) can be broadly classified based on shape into classical (saccular, or berry), fusiform and dissecting aneurysms, each with distinctive pathophysiology[1,2]. Saccular aneurysms comprise ninety percent of all cerebral aneurysms[3].

3.1.1. Localization and prevalence

Although aneurysms can potentially form anywhere, IAs are most commonly found at the base of the brain, namely on the circle of Willis[3]. Specifically, they form near areas of high hemodynamic stress, such as vessel bifurcations[1]. In the majority of cases, they form on the anterior portion of the cerebral circulation, specifically the Anterior Cerebral Artery (ACA) and Anterior Communicating Artery (ACommA), followed by the Medial Cerebral Artery (MCA), the Internal Carotid Artery (ICA) and Posterior Communicating Artery (PCommA), with only about 15% forming on the posterior portion of the circulation, i.e. the Vertebrobasilar Artery (VBA)[4]. Multiple IAs are present in about a quarter of the patients[5,6]. It has been estimated that around 3% of the adult population carry unruptured saccular aneurysms[7].

3.1.2. Etiology and risk factors

The majority of the aneurysms are thought to be – at least in part - the result of a congenital weakness in the vessel wall, specifically the tunica media[6]. Other, rarer causes include infections leading to mycotic aneurysms; trauma; and arteriosclerosis.

Intracranial aneurysms are not a congenital disorder (i.e., the aneurysm itself is not present at birth[8]) but rather develop gradually. Several risk factors have been consistently shown to be associated with the formation of IAs, including hypertension, female sex, chronic alcohol use, smoking, and IAs in first-degree relatives[9,10]. The ethnic background of a patient has been associated with the incidence of aneurysmal subarachnoidal hemorrhage (aSAH)[11] and patients with certain inheritable connective tissue disorders - particularly autosomal dominant polycystic kidney disease[12] - also carry a higher risk of developing IAs.

3.1.3. Risk of rupture

Many prospective and retrospective studies have identified risk factors for the rupture of unruptured intracranial aneurysms (UIAs), albeit with varying levels of evidence. These include: Aneurysm size (being the most powerful risk factor[2]), younger patient age, aneurysm location (with posterior circulation aneurysms carrying a higher risk of rupture), previous aneurysmal SAH, hypertension, smoking, family history of IA, aneurysm growth rate and

irregular aneurysm morphology[2,9,13–15]. The largest meta-analysis of prospective cohort studies to date, including data of over 10'000 UIAs and 8000 patients and published in 2014, was used to develop the PHASES score estimating the absolute five-year risk of rupture based on six independent risk factors mentioned above[14].

3.1.4. Treatment

Treatment of an aneurysm consists of excluding it from the arterial circulation.

3.1.4.1. Endovascular Treatment

The most commonly used endovascular treatment method is the Guglielmi detachable coil system, delivering platinum coils with a microcatheter through a guiding catheter, usually by entering through the femoral artery. By densely packing the aneurysm cavity with coils, it is occluded and thrombosis forms in its cavity, effectively removing it from the circulation. Further technical advances such as stent-assisted coiling and flow-diversion stenting (by which the stent is placed in the parent artery, altering hemodynamics thereby leading to gradual thrombosis of the aneurysm), have allowed more aneurysms – such as those with a wide neck - to receive endovascular management[16–18]. Endovascular treatment by selective coiling can be considered as first-line treatment for intracranial aneurysms of the posterior circulation and for many anterior circulation aneurysms (except for the MCA) – in young patients however, a surgical approach may be discussed in an interdisciplinary setting as endovascular coiling is known to be associated with a higher percentage of recanalization over time[36,37].

3.1.4.2. Surgical Treatment

Surgical treatment, in particular clipping, involves a craniotomy followed by clipping of the base of the aneurysm with a titanium clip. This treatment method has evolved since its inception, particularly with the development of a wide variety of clips, minicraniotomy approaches such as minipterional and lateral supraorbital approaches, the use of intraoperative electrophysiological recordings of evoked potentials and the use of blood flowmeters[19]. Microsurgical clipping has been proven to be a safe and effective way to treat aneurysms with a low risk of recurrence[20].

Both treatment approaches have distinct benefits and drawbacks and the decision on how to best treat aneurysms remains a topic of debate, whereby individual characteristics, including aneurysm location and size as well as the clinical condition of each patient have to be taken into consideration[21].

3.2. Subarachnoid Hemorrhage

Subarachnoid Hemorrhage (SAH) accounts for about 5% of all strokes and ca. 80% of spontaneous SAHs are of aneurysmal origin[22] – although the leading cause for all SAHs remains trauma. Rarer causes of spontaneous SAH include the rupture of other vascular abnormalities such as arterio-venous malformations (AVMs), intracranial tumor hemorrhage, cerebral vein thrombosis or amyloid angiopathy[23]. If no bleeding source is detected in the initial diagnostic workup, one speaks of angiogram-negative SAH, as is discussed in detail in section 3.4.

3.2.1. Symptoms and diagnosis

SAH leads to a massive and sudden increase in intracranial pressure (ICP). Patients describe a sudden and very severe headache – described as the "first and worse" – which may be accompanied by nausea, vomiting, photophobia, nuchal rigidity and loss of consciousness[24]. Up to 40% of patients experience a sentinel headache, probably due to a "warning leak", and subsequently have an increased risk of developing severe SAH with a high mortality risk in the following weeks[6].

Diagnosis of SAH is most often accomplished radiologically, with computer tomography (CT) being the first choice due to its availability, speed and high sensitivity in the acute setting[25]. Alternatively, MR Imaging (MRI), especially susceptibility-weighted imaging (SWI) or fluid attenuated inversion recovery (FLAIR) is useful and more sensitive than CT in detecting subarachnoid blood components already several days old[26]. In case of negative CT and clinical suspicion of SAH, a lumbar puncture is indicated to reveal hemoglobin breakdown products[5]. Following the diagnosis of SAH, neurovascular imaging such as CT-Angiography or digital subtraction angiography is mandatory to detect the source of the SAH, as is discussed in section 3.3.

3.2.2. Prognosis

Several studies in different populations have placed the overall 30-day mortality of aneurysmal SAH at 30-40% and the dependency rate of the survivors at 50%[27–30]. Non-aneurysmal SAH patients, such as those suffering from a perimesencephalic SAH, have a better prognosis than aSAH patients, as discussed in section 3.4. Grading scores have been developed which provide a more exact prognosis based on the severity of the SAH, like the World Federation of Neurosurgeons Scale (WFNS), which is determined using the Glasgow Coma Scale (GCS) and the presence or absence of focal neurological deficits. The WFNS scale was conceived with the assumption that the most important predictor of mortality is conscious state[31]. Other established factors which influence prognosis include the patient's age, comorbidities and volume of the hemorrhage shown in the initial CT scan[9]. The Hunt

and Hess scale is based on the patient's clinical presentation and is used as a predictor of survival[32]. The Fisher scale, and more recently the modified Fisher scale, are common radiological grading systems based on the thickness and distribution of blood in the initial CT scan and correlate with vasospasm incidence[33,34].

3.2.3. Treatment and complications

The main goals of SAH treatment are the prevention of rebleeding as well as the treatment and prevention of other complications. The exclusion of the bleeding source from the circulation should be done as soon as possible so as to prevent rebleeding and allow safe treatment of vasospasms[9,35]. As with unruptured aneurysms, microsurgical or endovascular treatment are available, and treatment decisions are made on a case-by-case basis. Large, randomized trials have been performed in recent years to compare these two methods in the case of ruptured aneurysms, such as the International Subarachnoid Aneurysm Trial (ISAT), a randomized trial including over 2000 patients, and the Barrow Ruptured Aneurysm Trial (BRAT), which have provided insight into the short- and long-term outcomes of patients treated with either method.[9,36–40].

The three main complications of SAH are rebleeding, delayed cerebral ischemia (DCI) and hydrocephalus. Due to these events, the first two weeks after the SAH have especially high mortality and morbidity rates[38]. Other possible complications include seizures, electrocardiographic abnormalities and electrolyte imbalances.

The rebleeding risk is highest in the first days after SAH and rebleeding is associated with mortality rates of 50%[24,41]. The risk is reduced by early aneurysm treatment. The high blood pressures often found after SAH due to elevated ICP and sympathetic activation also increase rebleeding risk and should be treated pharmacologically to pressures of around 140-160mmHg[6,9]. There has been concern that lowering the blood pressure reduces brain perfusion due to the high ICP, and thus worsens clinical outcome. Studies addressing these concerns, however, did not find this to be the case[42,43].

The risk for DCI – which can occur with or without angiographically detectable vasospasm - is highest between days 7 and 10 after SAH and DCI significantly increases the risk of adverse outcome[6]. Detection of vasospasms can be done radiologically, i.e. using CT angiography or DSA. Transcranial ultrasound is a possibility for the monitoring of patients by measuring blood flow velocity in major vessels, with the ICA and MCA having the highest sensitivity[44]. The therapeutic approach to vasospasm is complex and subject to intense research. Nimodipine has been shown to improve neurologic outcome and should be given as prophylaxis to all patients with aSAH[35,45]. In case of symptomatic vasospasm, pharmacologically induced euvolaemic hypertension is recommended over the traditional

"triple H" therapy of hypertension, hypervolemia, and hemodilution[35,46]. Endovascular approaches such as balloon dilatation or injection of nimodipine are also a possibility, though data is sparse[9,35].

Hydrocephalus – occlusive or communicating - can develop up to two weeks after the SAH, can become chronic, and is easily detectable in a CT scan. Treatment usually consists of placing an extraventricular drain (EVD) or lumbar drain (LD), or in the case of chronic hydrocephalus, a ventriculoperitoneal shunt (VP-Shunt)[35].

3.3. Neurovascular Imaging

The field of neurovascular imaging aims at depicting the circulation of the brain and the spine. It is a rapidly evolving area with a multitude of techniques. In the context of SAH and aneurysms however, three techniques are of distinct importance: CT-Angiography (CTA), MR-Angiography (MRA) and Digital Subtraction Angiography (DSA).

3.3.1. CT-Angiography

CTA uses intravenous iodinated contrast agent to image vessels and can be performed immediately following the CT scan in which SAH is diagnosed. It enjoys excellent detection rates of nearly 100% for aneurysms larger than 3mm[25,47,48] and technological advancements are improving its detection capacity for smaller aneurysms and aneurysms close to the skull base[49]. As in the other imaging modalities, 3D reconstruction of the images is critically helpful in diagnosing vascular lesions and in characterizing their vascular anatomy. Overall, recent large studies have shown that the detection gap for aneurysms to DSA is closing[50,51], making CTA a vital tool for the rapid diagnostic workup needed following SAH. The main drawbacks of this technique are its use of a potentially nephrotoxic and anaphylactogenic contrast agent as well as its exposure to radiation.

3.3.2. MR-Angiography

Several methods exist in order to depict vessels using magnetic resonance imaging. These can be broadly classified into flow-based methods, which do not use contrast agents, and contrast-agent based methods, which use a gadolinium-containing contrast agent. The most commonly used flow-based method is Time-of-flight MRA (TOF-MRA).

A large meta-analysis published in 2014 provided important data on the diagnostic utility of MRA regarding aneurysms[52]. In particular, the diagnostic performance of TOF-MRA and contrast-enhanced methods were not significantly different, and 3 Tesla MR imaging performed better than 1.5 Tesla imaging. Moreover, the value of 3D reconstruction of the images was clearly demonstrated in this study, as it significantly improved diagnostic performance. Overall, aneurysms were detected with comparable sensitivity to CTA (95%)

but with a lower specificity of 89%, indicating a comparatively high number of false-positive findings. Due to its longer runtime, lesser availability and higher susceptibility to motion artifacts, MRA is rarely used in the acute setting.

3.3.3. Digital Subtraction Angiography

DSA is an invasive, catheter-based fluoroscopic technique by which an X-Ray contrast agent is directly injected into the artery in question, and the pre-contrast image is subtracted from the subsequent contrast films. DSA, especially 3D rotational angiography remains the gold standard for the detection of aneurysms thanks to its excellent, sub-millimeter spatial and high temporal resolution[5,47]. This resolution allows precise characterization of the relationship of the aneurysm to its parent artery and to any neighboring small arterial branches, which is crucial for the diagnostic workup of the patient and for the treatment decisions. As such, it remains the best diagnostic tool for the depiction of the vascular anatomy. DSA is associated with complications (such as stroke or vascular injury), however the rate of complications is low (ca. 0.3%) and most of these complications are not permanent[53]. Finally, DSA remains a time-consuming, expensive and somewhat invasive technique[5]. Similar to CTA, its additional limitations are the use of contrast agent and its exposure to radiation.

3.4. Angiogram-negative subarachnoid hemorrhage

Cases in which no bleeding source is visible in the initial imaging occur in up to 20% of the spontaneous SAH patients[54]. Over the course of the last 2 decades, it has become common in the literature to divide these patients into two subgroups. These two groups require different diagnostic and therapeutic approaches.

3.4.1. Perimesencephalic subarachnoid hemorrhage

Perimesencephalic subarachnoid hemorrhage (PM-SAH) is a distinct type of hemorrhage which is defined by the following criteria[55]: Subarachnoid blood located in the midbrain (pretruncal) cisterns, with its center directly anterior to the midbrain and with no extension of the hemorrhage to the lateral Sylvian fissures or to the anterior part of the interhemispheric fissure. Furthermore, no frank intraventricular hemorrhage (some sedimentation in the posterior horns is allowed) or extension of the hemorrhage into the brain parenchyma is permitted. The clinical symptoms upon bleeding are relatively mild, with patients fully conscious. As such, the bleeding source is believed to be of venous, as opposed to arterial, origin[56].

If the blood localization has been classified as perimesencephalic and no bleeding source has been determined in a high-quality CTA or DSA, no further diagnostic workup is necessary, as later re-imaging has consistently been shown to reveal bleeding sources only in very few patients, and the risk of the DSA procedure itself in particular outweighs its

diagnostic yield[57]. These patients enjoy excellent recovery and low complication rates, and as such can be discharged within a few days after bleeding and generally do not require long-term clinical follow-up[58–60].

3.4.2. Non-perimesencephalic subarachnoid hemorrhage

The patients with diffuse CT blood distribution which is not confined to the pretruncal cisterns form an etiologically heterogenous group termed non-perimesencephalic subarachnoid hemorrhage (NPM-SAH). Several publications have shown that these patients, contrary to PM-SAH patients, develop typical complications seen in aneurysmal SAH patients – in particular hydrocephalus and vasospasm, but also severe neurological deficits such as central facial palsy or hemiparesis - , albeit less frequently[61–65]. For this reason, patients with NPM-SAH are commonly treated akin to aneurysmal SAH patients.

The diagnostic yield of second-look imaging, especially using DSA, has been reported to be up to 20% in the recent literature[66–69], with a thrombosed or dissecting aneurysm a possible cause[70]. Rarer causes such as arteriovenous malformations (AVM), spinal vascular lesions or dural arteriovenous fistula have been described as well[22]. Based on these findings, the guidelines European Stroke Organization recommend re-imaging using CTA or DSA 3 weeks or later after bleeding, if there are no indications to perform it earlier[57].

It is vitally important to rule out a treatable etiology in these patients to prevent rebleeding, which is often lethal. However, the optimal protocol for follow-up imaging of patients with spontaneous NPM-SAH and initially negative vascular imaging is unclear. To this day, patients receive imaging to the discretion of the treating surgeon, with many institutions and hospitals having empirically developed individualized follow-up imaging and treatment protocols. In particular, the value of noninvasive alternatives to DSA like MRA remains largely unexplored in the literature, as does the optimal time to re-imaging after bleeding. These issues are at the heart of this study.

3.5. Research questions

The following research questions are addressed in this study:

1. When is neuroimaging needed after spontaneous, angiogram-negative NPM-SAH?
2. Is high-quality, 3 Tesla MRA a noninvasive alternative to DSA for follow-up imaging of NPM-SAH patients?

4. MATERIALS AND METHODS

4.1. Setting and patients

In this retrospective, single-center study, the medical records of patients with spontaneous, angiogram-negative NPM-SAH were reviewed. The University Hospital of Zurich (USZ) is a tertiary referral hospital to which patients with SAH are transferred from a large geographical area due to its neurosurgical treatment capabilities.

A list of patients treated in the USZ with NPM-SAH was compiled dating back to 2007. These patients were included based on the following criteria: Patients presenting themselves with spontaneous SAH diagnosed radiologically or through lumbar puncture, with no bleeding source in the first CTA and DSA and with the subarachnoid blood distribution not confined to the midbrain cisterns - i.e. reaching the lateral Sylvian fissures or the anterior part of the interhemispheric fissure -, or with intraventricular or intraparenchymal blood. Patients with traumatic brain or extensive head injuries were excluded from the analysis.

4.2. Data collection and statistical analysis

Data from the medical records of the included patients was collected. Demographic data such as age and gender, radiological data including the type and time of the diagnostic imaging and of the follow-up imaging, and clinical information such as neurological status on presentation, complications while hospitalized and relevant comorbidities was gathered. Day 0 was defined as the day the bleeding occurred.

The initial SAH severity was determined using the Hunt and Hess score, the WFNS score, the GCS at admission, and the Fisher scale.

The Hunt and Hess score

1	mild headache
2	Cranial nerve palsy/severe headache/nuchal rigidity
3	Mild focal deficit/lethargy/ confusion
4	Stupor/hemiparesis
5	Deep coma/decerebrate posturing

Table 1: The Hunt and Hess score

The WFNS score

Grade	GCS	Motor deficit
1	15	Absent
2	13-14	Absent
3	13-14	Present
4	7-12	Present or absent
5	3-6	Present or absent

Table 2: The WFNS score

The Fisher scale

1	No SAH visible radiologically
2	SAH thickness <1mm
3	SAH thickness >1mm, no intraventricular hemorrhage
4	Intraventricular or intraparenchymal hemorrhage

Table 3: The Fisher scale

Follow-up imaging was characterized based on the time it was performed post-bleeding, the imaging modality that was used and the presence of relevant findings.

Data was collected in Microsoft Excel in encrypted fashion in which the patients were assigned a neutral number, and a separate spreadsheet was compiled in which the neutral numbers were linked to the patient numbers of the USZ registry. All statistical analysis was done using SPSS Version 24.

To answer research question 1, re-imaging results were categorized into different time periods post-bleeding: short-term (0-2 weeks), medium-term (2-8 weeks), and long-term (>8 weeks). The negative predictive value of re-imaging during these time periods was calculated and used to gauge the need for further re-imaging beyond these time periods.

To address research question 2, the diagnostic yield of MRA and DSA was assessed, along with their respective negative predictive values. Furthermore, the positive predictive value of MRA was determined, as a marker for its reliability in detecting true aneurysms.

4.3. Ethics

The cantonal ethics committee of the canton of Zurich has approved this study under the Project ID **2018-02027** („*Re-imaging after spontaneous, non-perimesencephalic subarachnoid hemorrhage with initially negative angiogram: which type of neuroimaging is needed, and when?").* The application for this project used the template „Weiterverwendung biologischen Materials und/oder gesundheitsbezogener Personendaten für die Forschung bei fehlender Einwilligung und Information nach Artikel 34 HFG", with Dr Esposito as the project leader.

Only patients who had no documented refusal to participate in clinical studies were included in this project. Furthermore, from 2016 onwards, only patients who filled out the form "Generalkonsent" of the University Hospital of Zurich were included, thereby consenting to the anonymous usage of their biological and clinical data for research purposes.

Anonymity was ensured by assigning each patient a neutral number during the data collection, and compiling a password-protected table in which the neutral numbers were assigned to the patient number of the USZ registry KISIM. Only the student and the supervisor Dr. Esposito had access to this table. Collected, encrypted patient data was always kept securely in password-protected files to which only the student and Dr. Esposito had access.

5. RESULTS

32 patients were initially included in this study. These patients were admitted to the USZ with spontaneous NPM-SAH for which no bleeding source on initial CT-Angiography (CTA) or Digital Subtraction Angiography (DSA) was detected.

5.1. Patient characteristics

Of the 32 patients included in the study, 13 were female and 19 were male. The mean age was 62, with a range of 31-97.

PATIENT CHARACTERISTIC		NUMBER OF PATIENTS
AGE		62.0 (range 31-97)
FEMALE:MALE		13:19 (40.6%:59.4%)
HUNT&HESS	I	12 (37.5%)
	II	13 (40.6%)
	III	1 (3.1%)
	IV	4 (12.5%)
	V	2 (6.3%)
WFNS	I	18 (56.3)
	II	8 (25%)
	III	0 (0%)
	IV	3 (9.4%
	V	3 (9.4%)
FISHER	I	1 (3.1%)
	II	2 (6.3%)
	III	14 (43.8%)
	IV	15 (46.9%)
GCS	3-6	5 (15.6%)
	7-9	1 (3.1%)
	10-12	3 (9.4%)
	13-15	23 (71.0%)

Table 4: Patient Characteristics

5.2. Initial diagnostic imaging

All SAHs were diagnosed by CT or MR scans except in one patient for whom the SAH was detected by lumbar puncture, whereby the subarachnoid blood was then seen in an MRI/MRA exam one day after diagnosis.

All patients received a CTA scan as a first vascular imaging modality except for two patients: In one case, MRA was performed because of an allergy to CT contrast agent and renal insufficiency. In the other case, an MRI/MRA in which the SAH was initially diagnosed was

performed in a private practice as prescribed by the family physician after five days of cephalic pain.

In 4 cases, the initial CTA scan was performed in a peripheral hospital before the patient was transferred to the university hospital. In one of these cases, CTA was repeated in-house 3 hours after the first CTA once the patient had been transferred.

In all patients, the initial negative CTA or MRA after SAH diagnosis was followed within 24h by a DSA except in 6 cases: In one patient, DSA was not performed because of diabetic microangiopathy. Another patient developed severe renal insufficiency after the initial CTA. In three cases, the patients either died or their status was too critical to undergo DSA. In one patient, no explanation was found in the records for the omission of DSA at that point in time, although MRA was performed two days after the initial CTA and DSA subsequently one day later.

5.3. Clinical course

Of the 32 patients with angiogram-negative SAH, 30 patients received re-imaging, and two patients died from the bleeding before re-imaging could be performed.

All patients were treated in the ICU according to standard clinical practice for subarachnoid hemorrhage treatment. Of the patients receiving re-imaging, 2 died (6.7%, Table 5): One patient died of severe pneumonia twelve weeks after bleeding, while one patient died of cardiac arrest 15 days after bleeding.

15 patients (50%) developed hydrocephalus. Of these, 13 patients received an EVD, 7 patients a LD and 6 were finally treated with a VP Shunt. 4 patients (13.3%) experienced symptomatic vasospasm.

All but 3 patients were followed-up at least once clinically after 8 weeks: one patient was transferred to his home country after 15 days. One patient did not wish any more follow-ups after 40 days. The third patient died of cardiac arrest at day 15 as outlined above. However, the long-term clinical outcome of the patient series using either the modified Rankin Scale (mRS) or the Glasgow Outcome Scale (GOS) could not be adequately gathered due to the inconsistency of its documentation with these scales during clinical follow-up. None of the patients experienced re-bleeding during clinical follow-up (median 263 days, range 15-1517 days).

COMPLICATION	NUMBER OF PATIENTS
DEATH	2 (6.7%)
HYDROCEPHALUS	15 (50.0%)
EVD	13 (43.3%)
LD	7 (23.3%)
VP SHUNT	6 (20.0%)
SYMPTOMATIC VASOSPASM	4 (13.3%)
RE-BLEEDING	0 (0%)
MEAN DAYS IN ICU (DEATHS EXCLUDED)	12.5 (range 1-23)
MEAN DAYS IN HOSPITAL (DEATHS EXCLUDED)	18.75 (range 11-40)

Table 5: Clinical course

5.4. Re-imaging after bleeding

30 patients received re-imaging, consisting of CTA (12 patients), DSA (16 patients), 3 Tesla brain TOF-MRA (27 patients) and 3 Tesla neck TOF-MRA (3 patients). The three modalities were performed at different time points for each patient, and were often repeated for each patient.

Re-imaging revealed 3 true aneurysms (10.0% yield) and 2 false positive findings (6.7%).

For presentation, re-imaging was categorized into five time periods since bleeding: 1-7 days, 8-14 days, 2-8 weeks, 2 weeks-1 year, >1 year (Table 6).

FOLLOW-UP IMAGING MODALITY	DAYS SINCE HEMORRHAGE				
	1-7 days	8-14 days	15-56 days	57-365 days	>365 days
DSA: # OF EXAMINATIONS	4	10	5	2	
# OF PATIENTS	4	10	5	2	
TRUE POSITIVE	-	-	**2 detected 1 confirmed**	-	-
FALSE-POSITIVE	-	-	-	-	-
CTA: # OF EXAMINATIONS	6	7	3	5	
# OF PATIENTS	5	6	3	2	
TRUE POSITIVE	-	-	**1 confirmed**	-	-
FALSE-POSITIVE	**1**	-	-	-	-
MRA: # OF EXAMINATIONS	12	14	7	22	8
# OF PATIENTS	12	14	7	19	7
TRUE POSITIVE	-	-	**1 detected 2 confirmed**	-	-
FALSE-POSITIVE	-	**1**	-	-	-

Table 6: follow-up imaging by days after bleeding

For analysis, re-imaging was categorized into:

- short-term re-imaging: within the first 14 days after bleeding (during the acute phase, while the patient is still hospitalized)
- medium-term re-imaging: from two to eight weeks after bleeding
- long-term re-imaging: later than eight weeks after bleeding

5.4.1. True aneurysms

Regarding the three true aneurysms detected during follow-up imaging, an aneurysm of the pericallosal artery was shown in a DSA and in MRA 44 days after bleeding. In the second case, a basilar aneurysm was seen in a DSA 39 days and in MRA 44 days after bleeding. In the third case, a carotid paraclinoidal aneurysm was seen on MRA 20 days after bleeding, thereafter further confirmed by CTA and DSA (21st-23rd day). The pericallosal and the basilar aneurysms were determined to be the bleeding sources. The paraclinoidal aneurysm was shown intraoperatively not to be in the subarachnoid space and therefore not to be the source of the bleeding.

In these 3 cases, the first re-imaging was performed on day 1 (MRA, for the pericallosal aneurysm), on day 11 (CTA, for the basilar aneurysm), and on day 4 (CTA, for the paraclinoidal aneurysm). Before detection of the aneurysm, DSA re-imaging was performed only for the pericallosal aneurysm (day 5) and for the paraclinoidal aneurysm (day 8) (Table 7).

All these 3 true aneurysms could be identified on MRA as well as DSA. They were all detected during medium term re-imaging (2-8 weeks after bleeding).

FOLLOW-UP IMAGING MODALITY	DAYS SINCE BLEEDING				
	1-7 days	8-14 days	2-8 weeks	8 weeks – 1 year	>1 year
PATIENT 1 (PERICALLOSA)					
DSA:	day 5		**day 44**		
CTA:					
MRA:	day 1		**day 44**		
PATIENT 2 (BASILAR)					
DSA:			**day 39**		
CTA:		day 11	day 17		
MRA:			**day 44**		
PATIENT 3 (PARACLINOIDAL)					
DSA:		day 8	**day 21**		
CTA:	day 4		**day 23**		
MRA:	day 7		**day 20**		

Table 7: Follow-up imaging in the three patients with true aneurysms

5.4.2. False-positive findings

Concerning the two false positive imaging results (6.7%), one was seen in a CTA performed 2 days after bleeding, which was a dilation of the A1 segment of the ACA that was judged to be a potential aneurysm by the treating surgeon. In the second case, a saccular aneurysm at the bifurcation of the right MCA was suspected on MRA 11 days after bleeding. These two patients underwent surgical exploration, however intra-operatively no aneurysm was found. In both cases no DSA was performed before surgery, and in both cases the false-positive finding was found in the first re-imaging instance, during short-term follow-up (within two weeks after bleeding).

The positive predictive value (PPV) of MRA re-imaging in the first eight weeks was therefore 75% (3 true positives / (3 true positives + 1 false positive), while that of CTA was 50 % (1 true positive / (1 true positive + 1 false positive).

5.4.3. Negative predictive values

23 patients received MRA re-imaging at short term follow-up (within 14 days after bleeding). 7 patients received MRA re-imaging at medium term follow-up (from day 15th to 8 weeks after bleeding), for a total of 24 patients receiving MRA re-imaging from day 1 to week 8. 19 patients received long-term MRA follow-up (>8 weeks post-bleeding) (table 6).

The negative predictive value (NPV) of MRA re-imaging in the first two weeks after bleeding was 91.3% in our series (21/23 = 21 true negatives / (21 true negatives + 2 false negatives)). The NPV of MRA at medium-term re-imaging was 100% (4 true negatives / 4 true negatives) as no relevant lesions were found in long-term MRA follow-up (19 patients).

14 patients received DSA re-imaging at short term follow-up (within 14 days after bleeding). 5 patients received DSA re-imaging at medium term follow-up (from day 15th to 8 weeks after bleeding) and 2 patients received DSA after eight weeks (table 6).

The NPV of DSA in the first 2 weeks was 85.7% (12 true negative / 12 true negative + 2 false negative), and, similarly to MRA, reached 100% at 8 weeks (2/2).

6. DISCUSSION

6.1. Key findings

30 patients with spontaneous, angiogram-negative NPM-SAH who received re-imaging were included in this retrospective study. Re-imaging revealed three true aneurysms, resulting in a diagnostic yield of 10.0%. All three aneurysms were detected during the period of medium-term re-imaging, which was defined as 2-8 weeks after bleeding, and all three aneurysms were visible both on MRA and on DSA. Two of these aneurysms were determined to be the bleeding source of the SAH.

The negative predictive value of DSA and MRA at day 14 post-bleeding was 85.7% and 91.3%, respectively, and reached 100% for both imaging modalities at 8 weeks post-bleeding. No relevant findings were seen during long-term re-imaging after 8 weeks in any of the 20 patients receiving follow-up imaging in that time period.

Re-imaging lead to two false-positive findings (one on CTA and one on MRA) in which both patients underwent surgical exploration which did not reveal an aneurysm. This resulted in a positive predictive value of 75% for MRA and 50% for CTA at 8 weeks. Neither patient had undergone a DSA examination prior to the surgical exploration.

6.2. Comparison with the recent literature

6.2.1. Value of MRA re-imaging

The literature has consistently shown the diagnostic value of re-imaging in NPM-SAH patients, especially of re-imaging using DSA. Two meta-analysis published in 2014 and 2017, investigating the yield of repeat DSA in this patient group have placed the diagnostic yield of repeat DSA at 10.0% (368 total patients)[66] and 12.6% (556 total patients)[71] respectively – although there was considerable variation in the diagnostic yield as well as sample sizes of the included studies in both cases. We can confirm the value of DSA re-imaging, with all true aneurysms visible on DSA re-imaging, resulting in a diagnostic yield of this imaging modality in our series of 10.0%. Furthermore, both aneurysms determined to have been the bleeding source were first detected on DSA. However, as all true aneurysms in our series were visible on MRA imaging as well, our study supports the notion that high-quality 3T MRA might be considered as a non-invasive alternative to DSA for re-imaging of NPM-SAH patients.

This finding is in contrast to some of the recent publications which have often not been able to show the value of MRA re-imaging, although the quality of the data is wanting and inconsistent: details on MR sequences and on the timing of re-imaging after bleeding is frequently insufficiently reported. For example, a study published in 2015 by Yap et al.

reported no new lesions detected by MR re-imaging in 63 patients (both PM-SAH and NPM-SAH patients): the timing of the MR examination however is not reported; furthermore, the number of patients who received MR-angiography specifically (as opposed to MRI without angio sequences) is not stated, greatly limiting its informative value in this context. In this same study, DSA re-imaging of 17 NPM-SAH patients showed one dissecting supraclinoidal ICA aneurysm on day 10 post SAH. It is however not reported if MRA imaging was also performed in this patient after the aneurysm was diagnosed[72].

Fontanella et al. reported in 2011 that no vascular malformations were detected by MRA re-imaging 21-60 days post-bleeding in 61 NPM SAH patients. These same patients had already received a negative repeat DSA 11-20 days after bleeding and were part of a cohort of 72 NPM-SAH patients. DSA re-imaging of this same cohort of 72 patients between days 11-20 post-bleeding had revealed 9 aneurysms (12.5%)[67]. However, the patient data in this study dates from 1991-1999 and MRA specifications or the usage of 3D-reconstruction software are not reported.

Andaluz et al. similarly described in 2008 no additional information gained from MRA performed in a series of 47 NPM SAH patients dating from 1998-2003, although the time to MR imaging or the imaging specifications are not reported. It is also not described if lesions seen in repeat DSA examinations were also visible in MRA[68]. DSA re-imaging – although no information about its timing is presented - showed relevant lesions in 10 (21.3%) of these same NPM-SAH patients, including 5 aneurysms.

Maslehaty et al. reported in 2011 no diagnostic benefit of 3T TOF-MRA of the head and neck performed in the first 72h after SAH diagnosis in 132 NPM-SAH patients with negative initial DSA[73]. Among these same patients, 120 later underwent repeat DSA, which revealed 13 aneurysms (10.8%). However, the time to DSA re-imaging in these patients is not reported, and neither if MRA was performed in these patients after the diagnosis of the aneurysm. Furthermore, the relatively early timing of MRA imaging after bleeding does not allow the generalization of the findings of this study to other time periods post-bleeding.

There exists no prospective study comparing the diagnostic yield of DSA and MRA in the context of re-imaging of NPM-SAH patients, and in the absence of such higher-quality data it is not possible to assess the value of MRA as a noninvasive alternative to DSA with high certainty. The few retrospective studies which have addressed this question to date are, as outlined above, hardly conclusive and have for the most part insufficiently reported data. Therefore, although our results support the notion that MRA might be a useful alternative to the more invasive DSA procedure for follow-up imaging of NPM-SAH patients, more data on this subject is needed.

6.2.2. Timing of re-imaging

Data regarding the exact timing of repeat imaging in NPM-SAH patients is relatively sparse, with many publications addressing this issue only marginally. Indeed several studies focusing on the re-imaging of NPM-SAH patients do not accurately, or sufficiently, report time to re-imaging of their patients[71,73–77]. As such, many institutions have empirically developed their own re-imaging protocols for this distinct group of patients. The guidelines for the management of intracranial aneurysms and SAH of the European Stroke Organization, published in 2013, propose re-imaging 3 weeks after bleeding at the earliest, if no therapeutic indications exist to perform it earlier, albeit with Level of Evidence B[57].

Nonetheless, several publications within the last two decades have shown the value of re-imaging within the first two weeks specifically, especially of DSA[54,78–85]. Only few recent studies with relatively small sample sizes do not report any findings with DSA re-imaging during the first two weeks[48,66]. In our series, in all 30 patients receiving re-imaging within the first 14 days after bleeding (15 receiving DSA, 24 receiving MRA, 9 receiving both), no bleeding source was determined. Therefore, as three true aneurysms were found during later re-imaging, the negative predictive value of MRA in the first two weeks was 91.3%, while that of DSA was 85.7%, indicating the need for further diagnostic workup beyond this acute phase.

The value of medium-term imaging in the period of 2-8 weeks, on the other hand, is far less well examined in the literature, although some publications have reported relevant findings in that time period using DSA, such as Kumar et al. which found an aneurysm in 2 out of 17 NPM-SAH patients using DSA at 6 weeks, resulting in a 11.76% yield[86]. These patients had not received an earlier repeat DSA, as re-imaging at 6 weeks post-bleeding only was standard practice in this study's hospital.

In one of the largest retrospective studies reporting time to re-imaging dating from 2013, Dalyai et al. described a vascular bleeding source in 7 out of 89 NPM-SAH patients (7.7%) receiving a third DSA examination at 6 weeks[78]. The bleeding sources were five aneurysms, one AVM and one dural arteriovenous fistula. These same patients had already undergone a negative re-imaging DSA examination at 1 week post-bleeding. The authors of this paper advocate for an extensive follow-up imaging protocol consisting of DSA both at 1 week and 6 weeks post-bleeding.

Delgado et al., in a retrospective analysis published in 2014 focusing on the diagnostic yield of repeat imaging after 14 days (median 34, range 14-69 days) after presentation in angiogram-negative SAH patients, found a bleeding source in 2 of 27 NPM-SAH patients (7.4%)[87]. One case was an ICA aneurysm seen on day 14, while the other was a small

pontine AVM seen on day 20. All patients included in this study had also received repeat DSA on day 7 which was deemed normal. Of note, both bleeding sources were discovered using CTA as a re-imaging modality, and both were retrospectively visible on the repeat DSA performed on day 7. The authors conclude, also in light of the results from Dalyai et al. described above, that re-imaging both during and after the short-term period of 2 weeks after bleeding is warranted in this patient group.

Overall, the time to re-imagine remains a contentious issue[66,86]. The main argument for early re-imaging within the first 2 weeks is the prevention of re-bleeding through treatment of the bleeding source[66,88]. Indeed, the highest risk of re-bleeding is in the first few days after bleeding, and it carries a very poor prognosis. On the other hand, some authors cite the need to await the vasospasm period, the resorption of the hematoma around the aneurysm or the dissolution of a potential occluding thrombus inside the aneurysm as a reason to perform repeat neuroimaging after 4-6 weeks only[72,78,89]. In our series, the true aneurysms were discovered on days 20, 39 and 44 after SAH, and all three patients had already undergone multiple re-imaging examinations, with at least one of those examinations during the first 14 days. We therefore propose, in accordance with the findings in the literature, that patients should receive short-term re-imaging within the first 14 days after bleeding - ideally during days 10-14 in order to avoid the most common period of vasospasm occurring during the days 7-10 after SAH. If short-term re-imaging was inconclusive, medium-term re-imaging near the end of this period - for example between 6-8 weeks after SAH – is indicated as well.

Long-term follow-up of 20 patients (19 of them with MRA, one with DSA, and one patient receiving both imaging modalities) after 8 weeks revealed no new relevant pathologies in our study, and thus the negative predictive values of MRA and DSA reached 100% at 8 weeks, suggesting that long-term follow-up imaging is not indicated in these patients. This is in accordance with recent publications: although there exists only limited data on the diagnostic yield of neurovascular imaging later than 8 weeks after NPM-SAH, the few studies which have investigated this issue – in some cases performing re-imaging up to several years after bleeding - have all reported no relevant findings, and thus the authors unanimously discourage from performing it[83,90–92].

6.2.3. False-positive findings

Our false-positive findings resulted in a positive predictive value of 75% for MRA and 50% for CTA at 8 weeks, whereby patients were surgically explored with no prior DSA. The radiological findings were small or peripheral (A1 dilation and MCA bifurcation dilation), and we believe a DSA examination in these patients might have prevented unnecessary surgical exploration. This indicates that suspect or unclear findings on CTA or MRA, in particular

when small or peripheral, should best be corroborated on a diagnostic DSA examination before performing surgical exploration to avoid false-positive findings.

6.3. Limitations of this study

A clear limitation of this study is its retrospective character and its relatively modest number of patients, which limits its significance. Larger prospective trials would be helpful to determine the optimal time frame for re-imaging of NPM-SAH patients as well as the value of noninvasive neuroimaging alternatives to DSA in this setting.

6.4. Conclusions

1. We propose re-imaging for NPM-SAH patients not only during the first 14 days after bleeding (ideally 10 to 14 days), but also near the end of our medium-term imaging period (for example at 6-8 weeks after bleeding). In our series, all aneurysms were seen during the medium-term follow-up period, resulting in a negative predictive value MRA of 91.3% and of DSA of 85.7% during the first two weeks. This means short-term follow-up within 14 days is not sufficient to rule out an aneurysm and medium-term follow-up at 6-8 weeks is suggested..

2. We suggest high-quality 3 Tesla MRA imaging as a possible non-invasive alternative to DSA for re-imaging after NPM-SAH. In our series, all confirmed aneurysms could be seen in MRA.

3. In re-imaging after NPM-SAH, suspect or unclear findings on CTA or MRA are best corroborated on a DSA examination before performing surgical exploration to avoid false-positive findings. This is especially true for small or peripheral findings, as they were in our cases.

4. Long-term radiological follow-up after 8 weeks post-bleeding did not produce diagnostic information in our series and is unlikely to be of diagnostic benefit. The negative predictive values of MRA and DSA both reached 100% at 8 weeks.

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8. APPENDIX

RE-IMAGING MODALITY	INSTANCE THE MODALITY WAS REPEATED					
	1st	2nd	3rd	4th	5th	6th
DSA: #OF PATIENTS	16	2	1			
MEAN DAY POST-ICTUS (RANGE)	9.75 (5-15)	33.5 (23-44)	66			
TRUE-ANEURYSMS	**1**	**2**				
FALSE-POSITIVES						
CTA: #OF PATIENTS	12	7	1	1		
MEAN DAY POST-ICTUS (RANGE)	15.4 (1-84)	39.8 (7-140)	169	246		
TRUE-ANEURYSMS						
FALSE-POSITIVES	**1**					
MRA HEAD: #OF PATIENTS	27	21	8	3	3	1
MEAN DAY POST-ICTUS (RANGE)	22.8 (1-117)	124.5 (12-490)	281.8 (23-987)	326 (109-557)	637 (297-922)	654
TRUE-ANEURYSMS	**1**	**2**				
FALSE-POSITIVES	**1**					
MRA NECK: # OF PATIENTS	3					
MEAN DAY POST-ICTUS (RANGE)	9.3 (6-15)					

Appendix Table: follow-up imaging by instance

9. CURRICULUM VITAE

Name, Vorname	Dufour, Jean-Philippe	
Geschlecht:	M	
Geburtsdatum:	31.12.1995	
Heimatort und Kanton	Genève, GE	
Ausbildung:	Primarschule:	Lycée Français de Zurich, 2007
	Mittelschule:	Literargymnasium Rämibühl, Zürich, 2013
		Matura: 5.45, International Baccalaureate: 41/45
	Universität:	Universität Zürich, 2013 – heute
	Medizinstudium:	Universität Zürich, 2013 - heute

10. ERKLÄRUNG

Masterarbeit

Ich erkläre ausdrücklich, dass es sich bei der von mir im Rahmen des Studiengangs

Humanmedizin

eingereichten schriftlichen Arbeit mit dem Titel

Repeated neuroimaging after spontaneous, non-perimesencephalic subarachnoid hemorrhage with initially negative angiogram: what kind of neuroimaging is needed, and when?

um eine von mir selbst und ohne unerlaubte Beihilfe sowie *in eigenen Worten* verfasste Masterarbeit* handelt.

Ich bestätige überdies, dass die Arbeit als Ganzes oder in Teilen weder bereits einmal zur Abgeltung anderer Studienleistungen an der Universität Zürich oder an einer anderen Universität oder Ausbildungseinrichtung eingereicht worden ist.

Verwendung von Quellen

Ich erkläre ausdrücklich, dass ich *sämtliche* in der oben genannten Arbeit enthaltenen Bezüge auf fremde Quellen (einschliesslich Tabellen, Grafiken u. Ä.) als solche kenntlich gemacht habe. Insbesondere bestätige ich, dass ich *ausnahmslos* und nach bestem Wissen sowohl bei wörtlich übernommenen Aussagen (Zitaten) als auch bei in eigenen Worten wiedergegebenen Aussagen anderer Autorinnen oder Autoren (Paraphrasen) die Urheberschaft angegeben habe.

Sanktionen

Ich nehme zur Kenntnis, dass Arbeiten, welche die Grundsätze der Selbstständigkeitserklärung verletzen – insbesondere solche, die Zitate oder Paraphrasen ohne Herkunftsangaben enthalten –, als Plagiat betrachtet werden und die entsprechenden rechtlichen und disziplinarischen Konsequenzen nach sich ziehen können (gemäss §§ 7ff der Disziplinarordnung der Universität Zürich sowie §§ 51ff der Rahmenverordnung für das Studium in den Bachelor- und Master-Studiengängen an der Medizinischen Fakultät der Universität Zürich.)

Ich bestätige mit meiner Unterschrift die Richtigkeit dieser Angaben.

Datum: 14.01.2019

Name: Dufour Vorname: Jean-Philippe

Unterschrift:……..*nur auf Printversion erforderlich*